

PATENT COOPERATION TREATY

RECEIVED

JUL 10 2008

HAYNES AND BOONE, LLP

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
TODD MATTINGLY
901 MAIN STREET
SUITE 3100
DALLAS, TX 75202

Date of mailing
(day/month/year)

Applicant's or agent's file reference
35449.15

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US05/18437

International filing date
(day/month/year) 25 May 2005 (25.05.2005)

Applicant
ENDOTHELIX, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70.

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Max Hindenburg
Telephone No. (571)-272-4726

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

Docketed: 7/10/08

File transferred out

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
TODD MATTINGLY
901 MAIN STREET
SUITE 3100
DALLAS, TX 75202

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year) **03 JUL 2008**

Applicant's or agent's file reference
35449.15

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US05/18437

International filing date
(day/month/year) 25 May 2005 (25.05.2005)

Applicant
ENDOTHELIX, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70.

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest against payment of (an) additional fee(s) under Rule 40.2,** the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer

Max Hindenburg

Telephone No. (571)-272-4726

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 35449.15	FOR FURTHER ACTION		see Form PCT/ISA/220 as well as, where applicable, item 5 below
International application No. PCT/US05/18437	International filing date (<i>day/month/year</i>) 25 May 2005 (25.05.2005)	(Earliest) Priority Date (<i>day/month/year</i>) 26 May 2004 (26.05.2004)	
Applicant ENDOTHELIX, INC.			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the **language**, the international search was carried out on the basis of:



the international application in the language in which it was filed.



a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 Rule 43.6 *bis(a)*

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (See Box No. III)

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/18437

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **A61B 5/00**(2006.01),**5/02**(2006.01),**6/00**(2006.01)

USPC: 600/474,493,549

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/300, 306, 412, 438, 474, 493, 549, 555

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,634,468 A (Platt et al.) 03 June 1997 (03.06.1997), see entire document	1-330
X	US 6,447,460 B1 (Zheng et al.) 10 September 2002 (10.09.2002), see entire document	1-7, 10, 13, 15-19, 23-31, 33-44
---		-----
Y		8-9, 11-12, 14, 20-22
A	US 5,050,612 (Matsumura) 24 September 1991 (24.09.1991), see entire document	1-330
A	US 6,547,745 B1 (Rubinstein) 15 April 2003 (15.04.2003), see entire document	1-330



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

12 June 2008 (12.06.2008)

Date of mailing of the international search report

03 JUL 2008

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Authorized officer

Max Hindenburg

Telephone No. (571)-272-4726

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/US05/18437

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0019269 A1 (Schaefer et al.) 29 January 2004 (29.01.2004), see entire document	79-81, 85, 97, 99-100, 106, 111-112, 114, 116-118, 120, 123, 131-132, 134, 138- 139, 142-143, 154, 155, 164, 167, 182, 185-188, 193-206, 208-210, 212-214, 216-217, 219-221, 223-229, 231-233, 235-237, 239, 242- 251, 258-262, 265- 273, 280-287
Y	US 4,428,382 (Walsall et al.) 21 January 1984 (21.01.1984), see entire document	48, 189-191 & 297- 298 & 300-307
Y	US 6,332,867 B1 (Chen et al.) 25 December 2001 (25.12.2001), see entire document	144-152, 252, 290- 291, 313-315
Y	US 3,463,854 (Kopjas) 26 August 1969 (26.08.1969), see entire document	317-329
Y	US 6,077,228 A (Schonberger) 20 June 2000 (20.06.2000), see entire document	48 & 297-298
Y	US 6,090,050 A (Constantinides) 18 July 2000 (18.07.2000), see entire document	276-279
Y	US 4,379,461 (Nilsson et al.) 12 April 1983 (12.04.1983), see entire document	160-163, 175, 316
Y	US 6,240,306 B1 (Rohrscheib et al.) 29 May 2001 (29.05.2001), see entire document	46, 47, 49, 51-54, 60- 62, 64, 69, 107, 140- 141, 254-255
X	WO 2004/017905 A2 (Kaharalkar et al.) 04 March 2004 (04.03.2004), see entire document	45, 50, 55-59, 63, 65- 68, 70-71, 74-78, 82- 84, 86-93, 96, 98, 101- 105, 107-110, 113, 115, 119, 121-122, 124-130, 133, 135- 137, 153, 156, 165- 166, 168-172, 176- 181, 183-184, 192, 203, 207, 211, 215, 218, 222, 226, 230, 234, 238, 240-241, 253, 256-257, 263- 264, 288-289, 292- 294, 299, 308-312 & 330

Y		79-81, 85, 97, 99-100, 106, 111-112, 114, 116-118, 120, 123, 131-132, 134, 138- 139, 142-143, 154, 155, 164, 167, 182, 185-188, 193-206, 208-210, 212-214, 216-217, 219-221, 223-229, 231-233, 235-237, 239, 242- 251, 258-262, 265- 273, 280-287

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
TODD MATTINGLY
901 MAIN STREET
SUITE 3100
DALLAS, TX 75202

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 35449.15		Date of mailing (day/month/year) 03 JUL 2008
International application No. PCT/US05/18437		FOR FURTHER ACTION See paragraph 2 below
International filing date (day/month/year) 25 May 2005 (25.05.2005)	Priority date (day/month/year) 26 May 2004 (26.05.2004)	
International Patent Classification (IPC) or both national classification and IPC IPC: A61B 5/00(2006.01),5/02(2006.01),6/00(2006.01) USPC: 600/474,493,549		
Applicant ENDOTHELIX, INC.		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

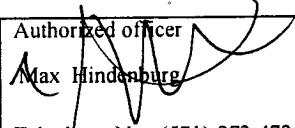
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 13 June 2008 (13.06.2008)	Authorized officer  Max Hindenburg Telephone No. (571)-272-4726
--	---	--

Form PCT/ISA/237 (cover sheet) (April 2007)

DUCKETED

7/10/08

By: caf

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US05/18437

Box No. 1 Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/18437

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>Please See Continuation Sheet</u>	YES
	Claims <u>1-7, 10, 13, 15-19, 23-31 & 33-44, 45, 50, 55-59, 63, 65-68, 70-71, 74-78, 82-84, 86-93, 96, 98, 101-105, 107-110, 113, 115, 119, 121-122, 124-130, 133, 135-137, 153, 156, 165-166, 168-172, 176-181, 183-184, 192, 203, 207, 211, 215, 218, 222, 226, 230, 234, 238, 240-241, 253, 256-257, 263-264, 288-289, 292-294, 299, 308-312 & 330</u>	NO
Inventive step (IS)	Claims <u>Please See Continuation Sheet</u>	YES
	Claims <u>Please See Continuation Sheet</u>	NO
Industrial applicability (IA)	Claims <u>Please See Continuation Sheet</u>	YES
	Claims <u>Please See Continuation Sheet</u>	NO

2. Citations and explanations:

Please See Continuation Sheet

1. **Claims 72-73** meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method for measuring a subject's endothelial functions by measuring and plotting a curve of skin temperature changes over time due to a provision of stimulant to a subject and measuring the area under the curve so as to thereby determine a health condition of the subject.
2. **Claims 274-275** meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method for measuring a subject's endothelial functions by calculating a ratio of a first, temperature dependent vascular reactivity parameter with a second, non-temperature dependent parameter so as to determine the health condition of the subject.
3. **Claims 1-330** meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/18437

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

V.1. Reasoned Statements:

The opinion as to Novelty was positive (Yes) with respect to claims 8-9, 11-12, 14, 20-22, 32, 46-49, 51-54, 60-62, 64, 69, 72-73, 79-81, 85, 94-95, 97, 99-100, 106, 111-112, 114, 116-118, 120, 123, 131-132, 134, 138-152, 154-155, 157-164, 167, 173-175, 182, 185-191, 193-202, 204-206, 208-210, 216-217, 219-221, 223-225, 227-229, 231-233, 235-237, 239, 242-252, 254-255, 258-262, 265-287, 290, 291, 295-298, 300-307 and 313-329

The opinion as to Novelty was negative (No) with respect to claims 1-7, 10, 13, 15-19, 23-31 & 33-44, 45, 50, 55-59, 63, 65-68, 70-71, 74-78, 82-84, 86-93, 96, 98, 101-105, 107-110, 113, 115, 119, 121-122, 124-130, 133, 135-137, 153, 156, 165-166, 168-172, 176-181, 183-184, 192, 203, 207, 211, 215, 218, 222, 226, 230, 234, 238, 240-241, 253, 256-257, 263-264, 288-289, 292-294, 299, 308-312 & 330

The opinion as to Inventive Step was positive (Yes) with respect to claims 72-73, 274-275

The opinion as to Inventive Step was negative (NO) with respect to claims 1-71, 74-273 and 276-330

The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-330

The opinion as to Industrial Applicability was negative (NO) with respect to claims NONE

V. 2. Citations and Explanations:

1. Claims 1-7, 10, 13, 15-19 & 23-44 lack novelty under PCT Article 33(2) as being anticipated by Zheng et al. (US 6,447,460).

Zheng et al. disclose a thermal energy measurement apparatus, comprising:
a thermal energy sensor 17 comprising a plurality of disposable energy sensors attached to the skin surface by adhesive for measuring skin temperature; wherein the thermal energy sensor comprises a thermistor; and
means 23 for coupling the thermal energy sensor to a skin surface of a body part, the coupling means operable to couple the thermal energy sensor to the skin surface of the body part while not substantially changing the skin surface temperature of the body part; wherein the means for coupling comprises a mesh having a non-insulating material and an airflow channel (i.e. opening from the mesh);
a computer system 13 coupled to the thermal energy sensor; wherein the computer is coupled to an alerting device (see figs. 2-4; col. 4, lines 7-47).

2. Claims 8-9, 11-12, 14 & 20-22 lack an inventive step under PCT Article 33(3) as being obvious over Zheng et al. (US 6,447,460).

Zheng et al. disclose a thermal energy measurement apparatus, as described above, that fails to explicitly teach a computer system coupled to a thermal energy sensor by a wireless connection, or a thermal measuring device comprising a ring, a watch, or a bracelet.

However, it is known to provide thermal measuring devices comprising a ring or bracelet (see fig. 1 of US 6,547,745) or a watch (see fig. 8 of US 5,050,612) or a computer system coupled to a miniature sensor by a wireless connection to emergency medical services (see abstract; see figs. 1, 3 & 7 & col. 2, lines 27-29 of US 5,634,468).

As such, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of Zheng et al. with a thermal measuring devices comprising a ring or bracelet or a or a computer system coupled to a thermal energy sensor by a wireless connection to emergency medical services since it is known to provide thermal measuring devices

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/18437

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

comprising a ring or bracelet or a or a computer system coupled to a thermal energy sensor by a wireless connection to emergency medical services.

3. Claims 45, 50, 55-59, 63, 65-68, 70-71, 74-78, 82-84, 86-93, 96, 98, 101-105, 107-110, 113, 115, 119, 121-122, 124-130, 133, 135-137, 153, 156, 165-166, 168-172, 176-181, 183-184, 192, 203, 207, 211, 215, 218, 222, 226, 230, 234, 238, 240-241, 253, 256-257, 263-264, 288-289, 292-294, 299, 308-312 & 330 lack novelty under PCT Article 33(2) as being anticipated by Kaharalkar et al. (WO 2004/017905).

Kaharalkar et al. disclose a method for determining one or more health conditions comprising:
providing a subject;
measuring the skin temperature on a distal location to the artery of a body part on the subject;
providing a vasostimulant to the subject;
measuring the skin temperature changes of the body part during and subsequent to the provision of the vasostimulant; wherein the vasostimulant is provided for less than 5 minutes; and
determining one or more health conditions for the subject based upon at least one of the skin temperature changes measured;
such that the method is fully monitors changes in the hemodynamic parameters parameters of a patient including temperature, blood flow and/or blood oxygen content, which are fully capable of assessing smooth muscle cells, tissue perfusion, risk of hypertension, diabetes, systemic inflammation (see claims 1-20 of Kaharalkar; see figs. 1-2; see abstract; see par 0002, 0004, 0011, 0018-0019, 0025).

4. Claims 157-159 lack an inventive step under PCT Article 33(3) as being obvious over Kaharalkar et al. (WO 2004/017905).

Kaharalkar et al. disclose a method, as described above, that fails to explicitly teach a thermal measuring device comprising a ring, a watch, or a bracelet.

However, it is known to provide thermal measuring devices comprising a ring or bracelet (see fig. 1 of US 6,547,745) or a watch (see fig. 8 of US 5,050,612).

As such, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of Kaharkar et al. with a thermal measuring device comprising a ring, a bracelet or a watch since it is known to provide thermal measuring devices comprising a ring or bracelet.

5. Claims 46, 47, 49, 51-54, 60-62, 64, 69, 107, 140-141, 254-255 lack an inventive step under PCT Article 33(3) as being obvious over Kaharalkar et al. (WO 2004/017905) in view of Rohrscheib et al. (US 6,240,306).

Kaharalkar et al. disclose a method, as described above, that fails to explicitly teach the step of applying a thermal energy source to heat the tissue.

However, Rohrscheib et al. disclose a method comprising the step of providing a vasostimulant to a subject either by applying a heat source or by applying a topical quantity of nitroglycerin onto the skin surface of a patient so as to induce vasodilatation for equilibrating the glucose or analyte concentration between the vascular system and the skin tissue and a step of measuring the patient's glucose after stabilization of the glucose level so as to provide a more accurate overall glucose concentration and predict the rate of glucose depletion or increase upon removal of the heating source (see col. 9, lines 38-46; col. 10, lines 7-45 & 51-56).

As such, it would have been obvious to one ordinary skill in the art at the time Applicant's invention was made to provide the method of Kaharalkar et al. with the step of heating the skin surface as taught by Rohrscheib et al. in order to induce vasodilatation for equilibrating the glucose or analyte concentration between the vascular system and the skin tissue and a step of measuring the patient's glucose after stabilization of the glucose level so as to provide a more accurate overall glucose concentration and predict the rate of glucose depletion or increase upon removal of the heating source.

6. Claims 160-163, 175, 316 lack an inventive step under PCT Article 33(3) as being obvious over Kaharalkar et al. (WO 2004/017905) in view of Nilsson et al. (US 4,379,461).

Kaharalkar et al. disclose a method, as described above, that fails to explicitly a method wherein the skin temperature is measured on a contralateral body part.

However, Nilsson et al. teach a method wherein contralateral skin temperatures are measured on both legs and calculating the differences between the two temperatures in order to diagnose the disturbances in circulation in the extremities of a patient (see abstract; see figs. 1-3).

Since Kaharalkar et al. teach a system for monitoring the changes in the hemodynamic parameters of a subject, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of Kaharalkar et al. with the step of measuring contralateral temperatures as taught by Nilsson et al. in order to diagnose the disturbances in circulation in the extremities of a patient.

7. Claims 48, 189-191 & 297-298 & 300-307 lack an inventive step under PCT Article 33(3) as being obvious over Kaharalkar et al. (WO 2004/017905) in view of Walsall et al. (US 4,428,382).

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/18437

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Kaharalkar et al. disclose a method, as described above, that fails to explicitly teach a method wherein the difference in temperature is used to assess whether the patient has cancer.

However, **Walsall et al.** teach that it is known to provide a method comprising the step of measuring the contralateral skin temperatures on both breasts and calculating the differences between the two temperatures in order to determine the presence or absence of asymmetry therebetween so as to determine the probable presence and location of normal or diseased tissue (i.e. breast cancer) when the difference is less than 0.6 or greater than 1 degree Celsius (see abstract; see fig. 1; see col. 3, lines 42-48; col. 13, lines 19-45); **Walsall et al.** further teach that it is known to provide a method of monitoring a patient's condition wherein the patient's body part is placed in water (i.e. ice) so as to produce regular cooling of normal tissue, while lesions with increased metabolism would exhibit decreased cooling pattern in localized areas and their relationship to the cooling rate of normal tissue is measured and used for diagnosis of the presence or absence of the lesion (see col. 6, lines 48-68; col. 7, lines 1-65); wherein the method further comprises the step of measuring a baseline body temperature (see col. 3, lines 9-19) such that a diseased tissue is diagnosed upon determination that the contralateral temperatures are greater than the reference temperature (see col. 13, lines 19-45).

As such, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of **Kaharalkar et al.** with the step of assessing the presence of cancer as taught by **Walsall et al.** in order to determine the probable presence and location of normal or diseased tissue (i.e. breast cancer) when the difference is less than 0.6 or greater than 1 degree Celsius.

Moreover, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of **Kaharalkar et al.** with the step of placing the patient's body part in water as taught by **Walsall et al.** in order to determine the probable presence of a lesion based on the decreased cooling rate and pattern.

Even moreover, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of **Kaharalkar et al.** with the step of measuring a reference temperature as taught by **Walsall et al.** in order to determine the presence of disease upon comparison of the respective contralateral body part temperatures to the reference temperature.

8. **Claims 276-279** lack an inventive step under PCT Article 33(3) as being obvious over **Kaharalkar et al.** (WO 2004/017905) in view of **Constantinides** (US 6,090,050).

Kaharalkar et al. disclose a method, as described above, that fails to explicitly a method wherein the difference in temperature is used to assess whether the patient has a diabetic foot.

However, **Constantinides** teaches that it is known to provide a method comprising the step of measuring the contralateral skin temperatures on both feet and calculating the difference between the two temperatures in order to determine the presence or absence of a diabetic foot (see figs. 1-2; see abstract; see col. 3, lines 47-61).

As such, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of **Kaharalkar et al.** with the step of assessing the presence of diabetic foot as taught by **Constantinides** in order to determine the probable presence diabetic foot.

9. **Claims 317-329** lack an inventive step under PCT Article 33(3) as being obvious over **Kaharalkar et al.** (WO 2004/017905) in view of **Kopjas** (US 3,463,854).

Kaharalkar et al. disclose a method, as described above, that fails to explicitly a step of measuring the effectiveness of a medication.

However, **Kopjas** teaches that it is known to provide a medication in controlled dosages to a plurality of subjects to determine the efficacy thereof through careful, scientific and extensive research on the subjects (see col. 2, lines 1-20 & 37-70; col. 5, lines 6-19).

As such, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of **Kaharalkar et al.** with the step of measuring effectiveness of a medication as taught by **Kopjas** in order to determine the efficacy the medication through careful, scientific and extensive research on the subjects.

10. **Claims 79-81, 85, 97, 99-100, 106, 111-112, 114, 116-118, 120, 123, 131-132, 134, 138-139, 142-143, 154, 155, 164, 167, 182, 185-188, 193-206, 208-210, 212-214, 216-217, 219-221, 223-229, 231-233, 235-237, 239, 242-251, 258-262, 265-273, 280-287** lack an inventive step under PCT Article 33(3) as being obvious over **Kaharalkar et al.** (WO 2004/017905) in view of **Schaefer et al.** (US 2004/0019269).

Kaharalkar et al. disclose a method, as described above, that fails to explicitly a plurality of known clinical testing methods for early detection of inflammation, viral and bacterial infections.

However, **Schaefer et al.** teach that it is known to test for inflammation, or viral/bacterial infection by monitoring the change in temperature of a body part of a patient (see abstract; see par 0003, 0005-0008, 0020-0021, 0031-0039).

As such, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of **Kaharalkar et al.** with the step of testing for inflammation of the body part as taught by **Schaefer et al.** in order to non-invasively detect the early stages of an inflammation.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/18437

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

11. Claims 48 & 297-298 lack an inventive step under PCT Article 33(3) as being obvious over Kaharalkar et al. (WO 2004/017905) in view of Schonberger (US 6,077,228).

Kaharalkar et al. disclose a method, as described above, that fails to explicitly teach the step of placing the patient's body part in water.

However, **Schonberger** teaches that it is known to provide a method of monitoring a patient's condition wherein the patient's body part is placed in water (i.e. ice) so as to produce regular cooling of normal tissue, while lesions with increased metabolism would exhibit decreased cooling pattern in localized areas and their relationship to the cooling rate of normal tissue is measured and used for diagnosis of the presence or absence of the lesion (see abstract; see col. 7, lines 5-59).

As such, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of Kaharalkar et al. with the step of placing the patient's body part in water as taught by Schonberger in order to determine the probable presence of a lesion based on the decreased cooling rate and pattern.

12. Claims 144-152, 252, 290-291, 313-315 lack an inventive step under PCT Article 33(3) as being obvious over Kaharalkar et al. (WO 2004/017905) in view of Chen et al. (US 6,332,867).

Kaharalkar et al. disclose a method, as described above, that fails to explicitly teach a step of measuring the patient's blood pressure.

However, **Chen et al.** teach method of measuring blood pressure in a manner that reduces the effects of white coat hypertension on the best estimate (see abstract; see figs. 1-2; see col. 10, lines 1-19).

Since Kaharalkar et al. teach a system for monitoring the changes in the hemodynamic parameters of a subject, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to provide the method of Kaharalkar et al. with the step of measuring blood pressure as taught by Chen et al. in order to measure blood pressure in a manner that reduces the effects of white coat hypertension on the best estimate.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- 1 [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers, claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
- 2 [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
- 3 [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4 [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.